

Highlights in head and neck cancer

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Locally advanced Squamous Cell carcinoma of the Head and Neck

Chemoradiation, radiation with cetuximab, chemoradiation with cetuximab, or accelerated radiation?

The combination of cetuximab and radiotherapy has never been compared to cisplatin-based chemoradiation in a randomised phase III trial. The Spanish Head and Neck Cancer Group (2007-01) treated patients with unresectable Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LA-HNSCC) with TPF (docetaxel, cisplatin, 5-fluorouracil) induction chemotherapy.¹ Patients responding after 2 or 3 cycles of TPF were randomised to receive radiotherapy (68-75 Gy in 35 fractions) with either cisplatin 100 mg/m² day 1, 22, and 42 (CRT) or weekly cetuximab (400 mg/m² loading dose followed by 250 mg/m²/week (400/250) (radiotherapy + cetuximab)). The primary endpoint was non-inferiority of radiotherapy + cetuximab versus CRT in terms of overall survival (OS). Assuming a median OS of 30 months with CRT and 32 months with CRT (hazard ratio [HR] = 0.938), 282 events were required to provide, with an α of 0.05, an 80% power to demonstrate non-inferiority, which was to be assumed if the upper limit of the one-sided 95% confidence interval (CI) of the HR for OS (radiotherapy + cetuximab/CRT) is below 1.3. Grade 3 or 4 mucositis (44.4% vs. 31.7%) and dermatitis (21.8% vs. 2%) occurred more frequently with radiotherapy + cetuximab. As expected, hematologic toxicity was more common with CRT. Grade 3 or 4 renal failure was slightly more common with CRT (1.5% vs. 1%). Renal failure of all grades was observed in 7.8% and 1.5% of the patients treated with CRT or

radiotherapy + cetuximab, respectively.

Eighty-five percent of the patients treated with CRT completed radiotherapy as planned versus 79% with radiotherapy + cetuximab. The OS rate at 3 years was 61.3% with CRT and 54.1% with radiotherapy + cetuximab (HR: 1.17). Progression-free survival (PFS) rate at 3 years was 50.3% with CRT and 41.3% with radiotherapy + cetuximab, respectively (HR: 1.2).

The results are inconclusive as the required number of events have not been reached due to better than expected survival rates in both arms.¹

In the GORTEC 2007-01 study, patients with stage III/IV, N0, N1, N2a or non-palpable N2b, LA-HNSCC, were randomised to receive radiotherapy (70 Gy in 35 fractions of 2 Gy) with either weekly cetuximab alone (400/250) or weekly cetuximab (400/250) plus carboplatin, 70 mg/m², followed by 5-FU, 600 mg/m²/day, day 1-4, in weeks 1, 4, and 7 (chemoradiation + cetuximab).² PFS (primary endpoint) at 3 years was 52.3% (95% CI 45-59) with chemoradiation + cetuximab versus 40.5% (95%CI: 34-48) with radiation + cetuximab (HR: 0.73 [95%CI: 0.57-0.94]; 2-sided log-rank p=0.015). There was no difference in distant metastases but locoregional control was significantly better with chemoradiation + cetuximab.²

The OCAT study enrolled patients with completely resected, previously untreated, locally advanced stage III/IV non-metastatic squamous cell carcinoma of the oral cavity with at least one of the following risk factors present in the surgical pathology report: extracapsular nodal extension, involvement of at least 2 regional lymph nodes, invasive cancer in the resection margin, exten-

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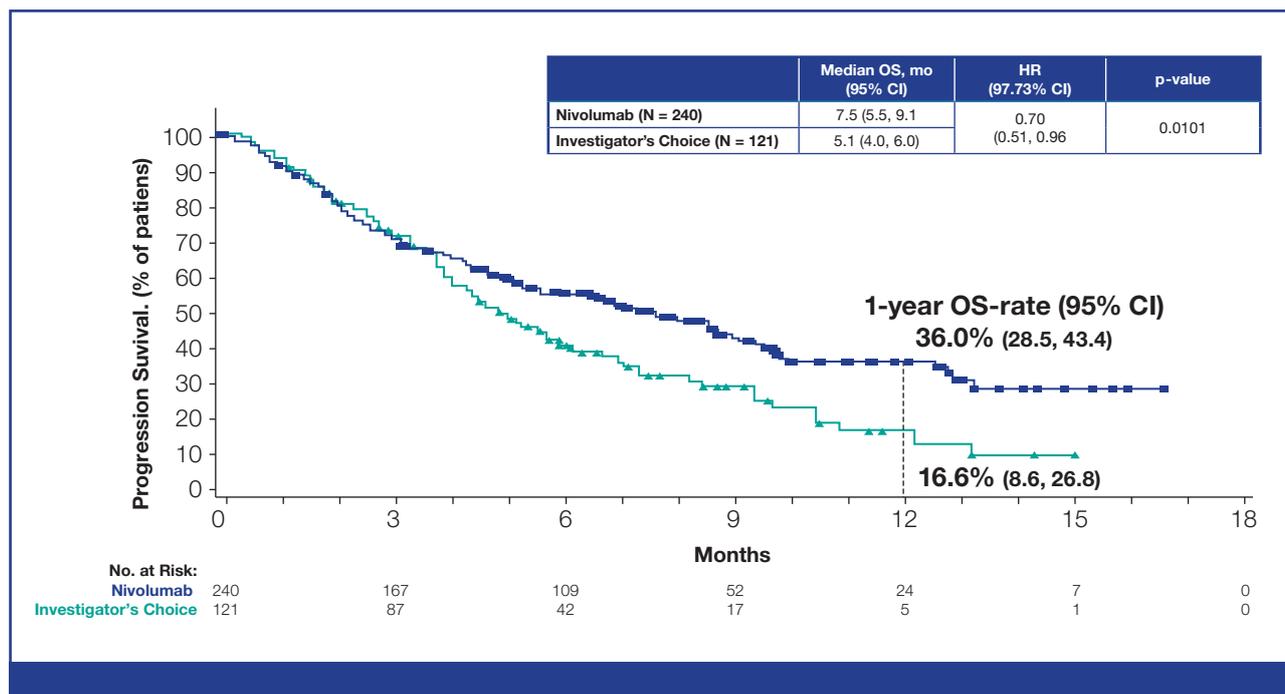


Figure 1. Overall survival in the phase III Checkmate 141 evaluating nivolumab in R/M HNSCC.⁶

sive soft tissue and/or skin involvement requiring major reconstruction, perineural invasion, or lymphovascular emboli.³ Patients were randomised to radiotherapy alone, 60 Gy in 30 fractions over 6 weeks, 5 fractions/week, or the same radiotherapy regimen in association with cisplatin, 30 mg/m²/week, or radiotherapy alone, 60 Gy in 30 fractions over 5 weeks, 6 fractions/week. Radiotherapy was delivered using conventional 2DRT with megavoltage photons. There was no significant difference in locoregional control rate or in acute toxicity between both treatment arms.³

Induction chemotherapy

In GORTEC 2007-02, patients with clinically palpable N2b, N2c, or N3 LA-HNSCC were randomised between chemoradiation (70 Gy in 35 fractions of 2 Gy with carboplatin 70 mg/m² followed by 5-FU 600 mg/m²/day, day 1-4, in weeks 1, 4, and 7) or 3 cycles of TPF followed by radiotherapy (70 Gy in 35 fractions of 2 Gy) with weekly cetuximab (400/250).⁴ No difference in PFS (primary endpoint) was observed between the treatment arms (HR: 0.93 [95%CI: 0.73-1.2]; 2-sided log-rank p=0.58). There was no difference in locoregional control, but distant disease-free survival (DFS) was significantly better with TPF followed by radiotherapy + cetuximab (HR: 0.62 [95%CI: 0.4-0.95]; p=0.03).⁴

The DeLos-II trial evaluated the impact of adding cetuximab to induction chemotherapy and radiotherapy on the 2-year functional laryngectomy-free survival in patients with resectable laryngeal and hypopharyngeal cancer. Patients were randomised to 3 cycles of TPF induction chemotherapy followed by radiotherapy (69.9 Gy) with (arm A) or without (arm B) weekly cetuximab (400/250) for 16 weeks throughout induction chemotherapy and radiotherapy.⁵

The primary objective of a 2-year functional laryngectomy-free survival rate above 35% was met in both arms (44.7% in arm A and 46.6% in arm B; odds ratio 0.93 [95%CI: 0.51-1.67]). More patients in arm A failed to respond to the first cycle of induction chemotherapy (31.8% vs. 22.7%).⁵

Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck

In Checkmate 141, patients with Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck (R/M HNSCC), progressing on or within 6 months of the last dose of platinum-based chemotherapy, were randomised 2:1 between nivolumab 3 mg/kg every 2 weeks or investigator's choice (methotrexate 40 mg/m²/week, or docetaxel 30 mg/m²/week, or weekly cetuximab [400/250]).⁶ At the pre-planned interim analysis, the median OS was 7.5 months (95%CI: 5.5-9.1)

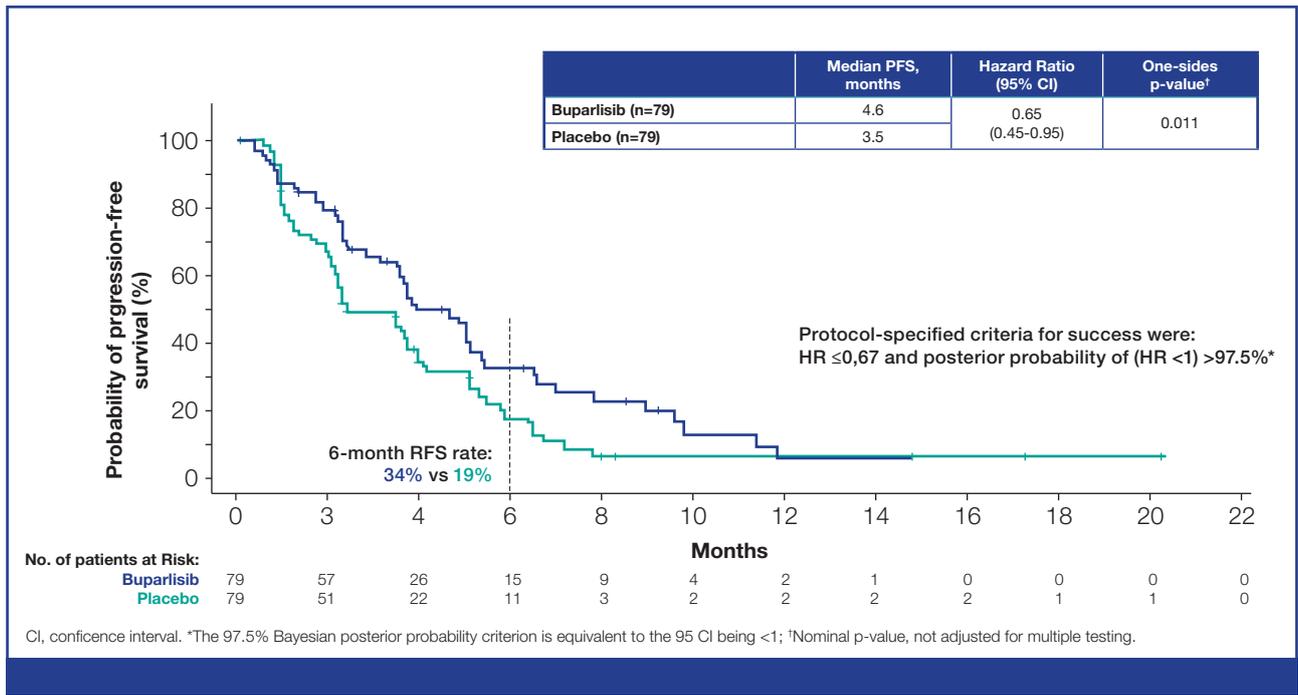


Figure 1. Buparlisib added to paclitaxel prolongs the PFS in patients with R/M HNSCC.⁹

with nivolumab vs. 5.1 months (95%CI: 4.0-6.0) with investigator's choice (HR: 0.70 [95%CI: 0.51-0.96]; p=0.0101) (Figure 1). The HR for OS was 0.55 (95% CI: 0.36-0.83) in patients with PD-L1 expression $\geq 1\%$ and 0.89 (0.54-1.45) in patients with PD-L1 <1%. The 1-year OS rate was 36% (95%CI: 28.5-43.4) and 16.6% (95%CI: 8.6-26.8), respectively. The median PFS was similar between the two arms (2.0 vs. 2.3 months with nivolumab and investigator's choice, respectively). The 6-months PFS rate was 19.7% (95%CI: 14.6-25.4) and 9.9% (95%CI: 5-16.9), with an overall response rate (ORR) of 13.3% (95%CI: 9.3-18.3) and 5.8% (95%CI: 2.4-11.6), respectively.⁶

Also pembrolizumab has shown promising antitumor activity and durable responses in R/M HNSCC. Mehra *et al.* presented a pooled analysis of the efficacy and safety of pembrolizumab after long-term follow-up of R/M HNSCC patients included in the Keynote-012 trial.⁷ In the initial cohort, 60 patients with PD-L1 positive tumours received 10 mg/kg every 2 weeks, whereas in the expansion cohort, 132 PD-L1-positive and -negative tumours were treated at a dose of 200 mg every 3 weeks. The ORR in this study was 17.7% (95%CI: 12.6-23.9). With a median follow up in responders of 12.5 months (range 8.4-24.4), the median duration of response was not yet reached. The ORR was 21.9% (95%CI: 12.5-34.0) in HPV-positive patients and 15.9% (95%CI: 10.0-

23.4) in HPV-negative tumours. The reported median OS was 8.5 months (95%CI: 6.5-10.5) with a 12-month OS rate of 38%.⁷ Finally, after 6-months 24.9% of the patients treated with pembrolizumab were still free of progression.

In another study, Chow *et al.* scored PD-L1 and PD-L2 in tumour cells and inflammatory cells of the R/M HNSCC patients enrolled in Keynote-012.⁸ When tumour and inflammatory cells were used to score PD-L1 status, an increase in ORR (p=0.023) and a longer PFS (p=0.026) and OS (p=0.008) were observed in patients with PD-L1-positive tumours. The ORR was higher in PD-L2-positive tumours and the IFN- γ gene signature score was found to be significantly associated with ORR, PFS, and OS (p<0.001). The HPV status did not predict PD-L1 positivity or expression of the IFN- γ signature.⁸

Buparlisib is a pan-inhibitor of the phosphatidylinositol 3-kinase (PI3K) pathway, which is frequently activated in HNSCC. In a randomised phase II trial conducted by Soulieres *et al.*, a total of 158 patients with R/M HNSCC, progressing after platinum-based therapy, were randomised 1:1 to receive paclitaxel 80 mg/m²/week with either buparlisib, 100 mg/day, or placebo.⁹ With the addition of buparlisib, the median PFS (primary endpoint) was improved from 3.5 to 4.6 months (HR: 0.65 [95%CI: 0.45-0.95]) (Figure 2). The median OS at

data cut-off was 10.0 vs. 6.5 months (HR: 0.71 [95%CI: 0.46–1.1]). Grade 3/4 adverse events which occurred more frequently in the buparlisib arm included hyperglycaemia (22% vs. 3%), anaemia (18% vs. 12%), neutropenia (17% vs. 5%), and fatigue (8% vs. 10%).⁹

Nasopharyngeal Cancer

Nimotuzumab is a humanised anti-EGFR monoclonal antibody. Kong *et al.* randomised 155 stage III/IVb nasopharyngeal carcinoma patients to receive radiotherapy (70 Gy in 35 fractions) with either cisplatin 40 mg/m²/week or nimotuzumab 200 mg/week after prior TPF induction chemotherapy.¹⁰ The primary endpoint consisted of the rate of grade 3/4 radiation-induced skin and mucosal toxicity. A sample size of 320 patients would provide an 80% power to detect a 15% difference in the primary endpoint (from 40% to 25%) with an α of 0.05. At the planned interim analysis after recruitment of 50% of the planned patient population, there was no statistically significant difference in grade 3/4 mucositis/dermatitis (40.2% with chemoradiation vs. 28.8% with radiation + nimotuzumab; $p=0.191$). Gastrointestinal and haematological toxicities were significantly more common with chemoradiation. Finally, the PFS and OS rates were similar in both treatment arms.¹⁰

Zhang *et al.* randomly assigned 362 patients with recurrent or metastatic nasopharyngeal carcinoma to gemcitabine 1 g/m² on days 1, 8, cisplatin 80 mg/m² on day 1, every 3 weeks, (GP) or 5-FU 4 g/m² as a continuous infusion over 96 hours and cisplatin 80 mg/m² on day 1, every 3 weeks, (FP) for up to 6 cycles.¹¹ The median PFS (primary endpoint) was 7 months in the GP group and 5.6 months in the FP group (HR: 0.55 [95% CI 0.44–0.68]; $p<0.001$). The reported ORR was 64.1% with GP as compared to 42% with FP ($p<0.001$). The median OS was 29.1 months with GP and 20.9 months with FP (HR: 0.62 95%CI: [0.45–0.84]; $p=0.002$). Grade 3/4 toxicities were observed in 37% and 32.4% of the patients with GP and FP, respectively ($p=0.41$). Adverse events leading to discontinuation of treatment occurred in 3.3% and 8.1% of the patients with GP and FP, respectively ($p=0.06$).¹¹

References

1. Hitt R *et al.* Randomised phase III trial of induction chemotherapy (ICT) with docetaxel-cisplatin-5-fluorouracil (DCF) followed by cisplatin-radiotherapy (CRT) or cetuximab-radiotherapy (CetRT) in patients (pts) with locally advanced unresectable head and neck cancer (LAUHCN). J Clin Oncol 2016;34(Suppl). Abstract 6001.
2. Bourhis J *et al.* Cetuximab-radiotherapy versus cetuximab-radiotherapy plus concurrent chemotherapy in patients with N0-N2a squamous cell carcinoma of the head and neck (SCCHN): Results of the GORTEC 2007-01 phase III randomised trial. J Clin Oncol 2016;34(Suppl). Abstract 6003.
3. Laskar SG *et al.* Phase III randomised trial of surgery followed by conventional radiotherapy (5 fr/Wk) (Arm A) vs concurrent chemoradiotherapy (Arm B) vs accelerated radiotherapy (6 fr/Wk) (Arm C) in locally advanced, stage III and IV, resectable, squamous cell carcinoma of oral cavity- oral cavity adjuvant therapy (OCAT): Final results. J Clin Oncol 2016;34(Suppl). Abstract 6004.
4. Geoffrois L *et al.* Induction docetaxel platinum 5-FU (TPF) followed by cetuximab-radiotherapy (cetux-RT) versus concurrent chemo-radiotherapy (CT/RT) in patients with N2b/c-N3 non operated stage III-IV squamous cell cancer of the head and neck (SCCHN): Results of the GORTEC 2007-02 phase III randomised trial. J Clin Oncol 2016;34(Suppl). Abstract 6000.
5. Dietz A *et al.* Final results of the randomised phase II DeLOS-II trial: Induction chemotherapy (IC) followed by radiotherapy (R) vs. cetuximab (E) plus IC and R for functional larynx preservation in resectable laryngeal and hypopharyngeal cancer (LHSCC). J Clin Oncol 2016;34(Suppl). Abstract 6025.
6. Ferris RL *et al.* Further evaluations of nivolumab (nivo) versus investigator's choice (IC) chemotherapy for recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): CheckMate 141. J Clin Oncol 2016;34(Suppl). Abstract 6009.
7. Mehra R *et al.* Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): Pooled analyses after long-term follow-up in KEYNOTE-012. J Clin Oncol 2016;34(Suppl). Abstract 6012.
8. Chow LQMC *et al.* Biomarkers and response to pembrolizumab (pembro) in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). J Clin Oncol 2016;34(Suppl). Abstract 6010.
9. Soulières D *et al.* BERIL-1: A phase II, placebo-controlled study of buparlisib (BKM120) plus paclitaxel in patients with platinum-pretreated recurrent/metastatic head and neck squamous cell carcinoma (HNSCC). J Clin Oncol 2016;34(Suppl). Abstract 6008.
10. Kong L *et al.* Radiation plus concurrent nimotuzumab versus CDDP in locally advanced nasopharyngeal cancer: Results of a phase III randomised trial. J Clin Oncol 2016;34(Suppl). Abstract 6002.
11. Zhang L. *et al.* Gemcitabine plus cisplatin (GP) versus 5-FU plus cisplatin (FP) as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC): A randomised, open-label, multicenter, phase III trial. J Clin Oncol 2016;34(Suppl). Abstract 6007.